Proc. Indian natn. Sci. Acad., **58**, A, No. 4, 1992, pp. 287-311

VISHWAKARMA MEDAL LECTURE–1991

SIDELIGHTS ON SYNTHETIC DRUGS

A V RAMA RAO, F.N.A.

Indian Institute of Chemical Technology, Hyderabad 500 007, *India*

(*Delivered* on* 30 *December* 1991)

I regard it as a privilege to deliver the "1991 Vishwakarma Medal Lecture" of the Indian National Science Academy. In fact, I consider this to be a great honour. I would like to take this opportunity to enumerate some of the successes in industrial research that have come my way during the course of my research. This was not because I was especially fascinated by the subject in my early research carrier, but due to various circumstances that forced me to initiate developmental work for reasons of survival and to remain in research. I would like to take this opportunity to be frank and forthright about my experiences, which may make a few youngsters realise the need to undertake research which will contribute to the Industrial Scene of this country.

After my graduation in chemical technology (pharmaceutical and fine chemicals) from the Department of Chemical Technology of Bombay University in 1960, I realised the need to enhance my capability in organic chemistry, as its ramifications have a direct bearing on health, food, clothing, shelter, etc. I therefore approached Professor K Venkataraman, the then Director of National Chemical Laboratory and the doyen of organic chemistry with a request to guide my PhD research. It took me 3½ years of hard and sincere work to complete my PhD (Tech) degree. My work concentrated on natural product chemistry, especially on the colouring matters of the jackfruit tree (*Artocarpus heterophyllus*). To justify my degree of PhD in technology, I had to synthesise some analogues of Khellin, a potential antiasthmatic drug. Unlike many who go abroad to pursue their postdoctoral career, I followed Professor Venkataraman's advice and stayed with him for a few more years in NCL, and accepted the Scientist-B position in 1965. Incidentally, I was the first Scientist-B appointed in the organic chemistry division in NCL who had not been across the sea. Being married and having a child at that time, I felt that a regular or permanent job is a God-given gift and resolved to remain with KV. My immediate assignment with Professor Venkataraman was to solve the age-old problem on the structure of lac dye which I proved to be mixture of several compounds (laccaic acids a, b, c, d) (Chart I). This problem had motivated me to investigate other insect pigments such as kermesic acid, etc. I also fell in line with Professor Venkataraman's interests on synthetic dyes and solved some fascinating unsolved problems such as azo-hydrazo tautomerism of azo dyes derived from phenols and naphthols. Between 1960 and 1970 I was totally committed to academic research and I came to believe that industrial research meant a mediocre work that was carried out by industrial laboratories.

*at the Physical Research Laboratory, Ahmedabad. The typescript was received on 29 April 1992.

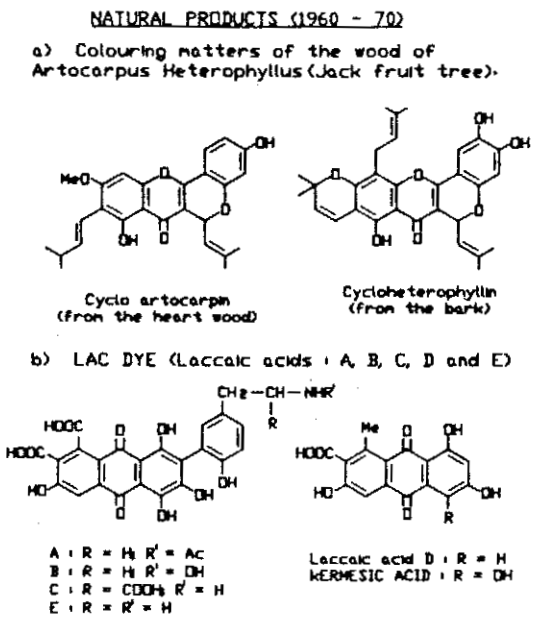


CHART I

In 1970, due to various reasons, Professor Venkataraman had entrusted me with the specific job of helping a small scale industry in Pune (Poona Synthetics). Poona Synthetics was started by a young entrepreneur, Mr Maharaj Singh, in 1968 mainly to manufacture the key intermediate *ortho*-tolunesulfonamide which goes into saccharine production. He was carrying out chlorosulfonation of toluene which gives *o*-toluenesulfonyl chloride and *p*-toluenesulfonyl chloride in the ratio of 40:60. The *o*-toluenesulfonyl chloride (liquid) is separated from PTS chloride (crystals) and both the acid chlorides were separately converted to their respective amides by treatment with ammonia. The OTS-amide is sold to saccharine manufacturers and the PTS-amide, a by-product was thrown aside in the factory. In the late 1960s when saccharine prices touched rock bottom due to its large scale production in Europe, many Indian manufacturers had to set OTS-amide at much lower prices than its production cost thereby incurring heavy losses. Professor Venkataraman felt that I was the right person to help this young entrepreneur and asked me to accept a consultancy assignment with the company mainly to revive the company's capability in finding new products and processes. When I first visited Poona Synthetics, I found nothing much in that factory but a heap of PTS-amide thrown aside. As they could not find any outlet for this by-product, it was being sold at a throw-away price of Rs 2 per kilo in those days. As he had no resources to diversify his activity, I felt that the only way of reviving the company was to find outlets for the so called "by-product". After two days of careful study, I felt the best way was to convert PTS-amide to its urethane derivative (Chart II) which could be converted to tolbutamide, a widely used anti-diabetic drug. When I suggested this to Mr Maharaj Singh, he gave the impression that it was difficult to sell this idea to Hoechst (India), Bombay as indigenous products normally

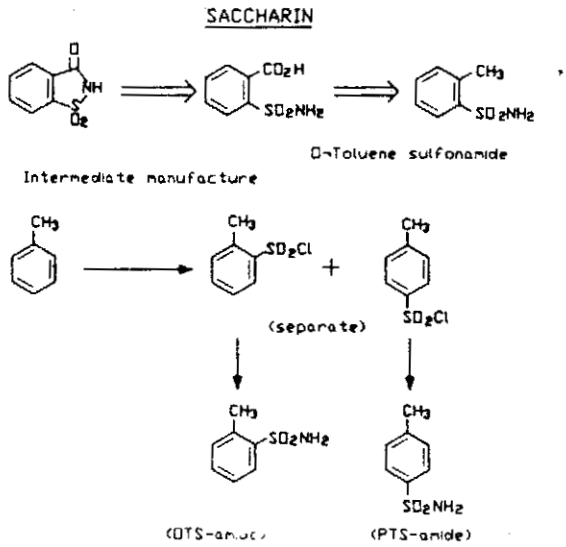


CHART II

failed to meet their stringent specifications, and hence Hoechst (India) continued to import it for its conversion to tolbutamide. We organised a small lab in Poona Synthetics to carry out developmental work on the urethane. I took the initiative of approaching Hoechst and impressed them about the quality of our product and our offer to provide it at a price lower than the imported product. This worked well and Hoechst placed an order with Poona Synthetics for the supply of 20 tonnes of urethane per annum. This gave me immense pleasure as it was my first assignment with industry and it had resulted in success. As the company faced problems in getting extra finance to implement this programme, I had to take the initiative to go to the State Bank of India and impressed on the Development Officer the need to sanction extra finance to revive the company and I personally assured them the financial viability in writing (which I realised later that I should not have done without the permission of the Director, NCL). I also had to design the plant and machinery required for producing this urethane with whatever chemical engineering knowledge I

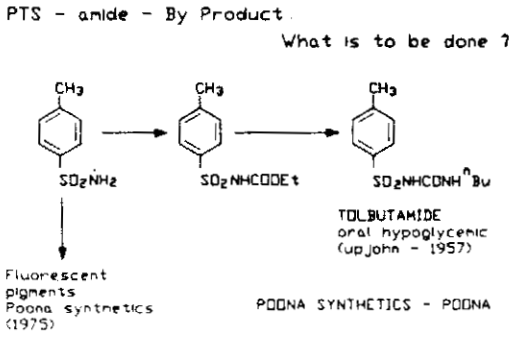


CHART III

had. I used to spend Saturdays and Sundays supervising the product batches on their premises which was 20 km away from Pune. We were all delighted to see that the first batch of 100 kilos of the urethane met all the stringent specifications (Chart III). With one year's production, the company was out of the red.

Our attention was then directed to finding other avenues for this so-called "by-product", PTS-amide, which was abundantly available from other Indian producers. After spending several evenings in the library, I realised that a large quantity of PTS-amide goes into the manufacture of fluorescent pigments. At that time India was importing at least 100 tonnes of fluorescent pigments, mostly from Japan. These pigments are used for printing textiles and also for the production of printing inks. Keeping this in mind, we struggled hard at Poona Synthetics to develop these pigments knowing very well that another Indian company had agreed to import the technology from a French company. These pigments are made by polymerisation of PTS-amide with formaldehyde and by adding 1% basic dye of the appropriate colour at the time of curing. The entire operation is very critical and calls for a thorough understanding of polymerisation.

The company developed over the course of two years, all the shades of fluorescent pigments except lemon yellow. The dye that was needed for this was very expensive and was supplied by only one American company. We worked with a coumarin derivative of a similar shade and with this Poona Synthetics achieved all the fluorescent pigment shades. These were commercialised in 1976.

My work with Professor Venkataraman since 1960 at NCL was totally confined to natural products and synthetic dyes despite the fact that NCL was going through a slow transformation from basic research to industrially oriented research as its goal. The then Director, Dr Tilak (1966-78) used to emphasise year after year the need to change our attitude towards industrial research. In fact, at some of the annual meetings he was rather aggressive while talking to some of the senior members of the organic chemistry division, insisting that fundamental research which had no relevance be stopped and industrial oriented projects be taken up to help the Indian Chemical Industry. Even though it caused quite a lot of bitterness among the chemists there was no alternative but to fall in line with the management. In one of the meetings in 1972, he directly pointed out to me stating that my research activity with Professor Venkataraman would not help me if I were to survive in NCL unless I initiated some programme on industrial research. This provoked me to initiate a project with another NCL colleague. Although Professor Venkataraman brushed aside Dr Tilak's annoyance towards me, I felt the need to initiate at least one project with which I could contribute to NCL's changed priority. As there were already established programmes on synthetic dyes, agrochemicals and perfumery chemicals, I felt the need to initiate a new programme in synthetic drugs, a branch which I had already learnt at UDCT. I spent several evenings in the library trying to understand the status of the Indian drug industry at that time, the prevailing patent laws which had just been amended to benefit the nation; wherein product patents were not permitted and process patents were cur-

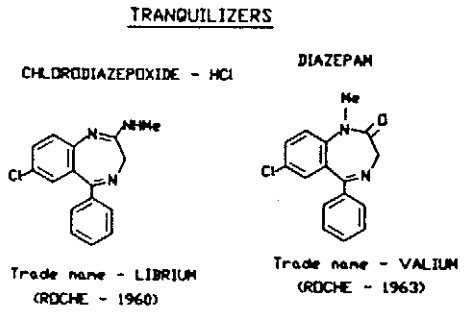


CHART IV

tailed to 5 years only if the product happended to be a drug or a pesticide. I thought of exploiting the new patent laws to my advantage by selecting a project on a value added drug. At that time, chlorodiazopoxide and diazepam were two best selling products worldwide (Chart IV). I selected diazepam as the product of my choice to initiate process development work for the benefit of the Indian drug industry. When I first approached the Director, NCL, and

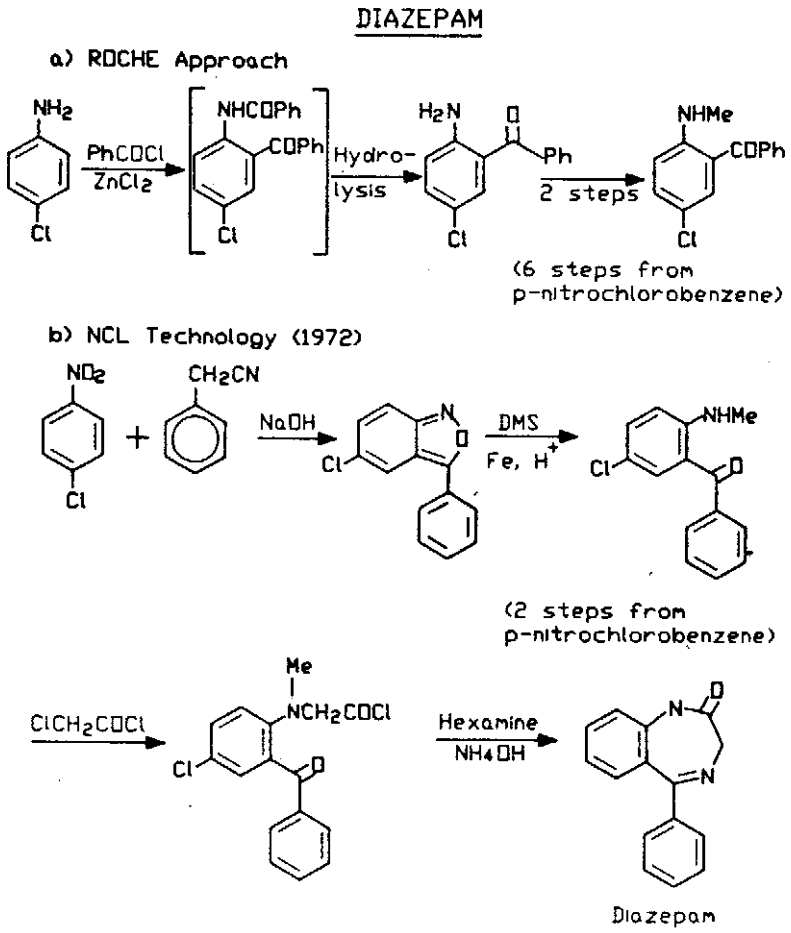
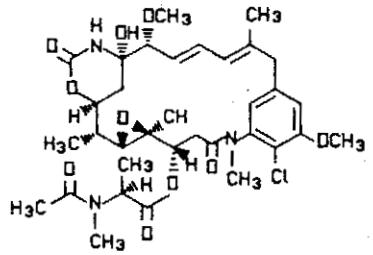


CHART V

indicated my interest in diazepam he was reluctant to approve the project as then RRL, Hyderabad had already undertaken sponsorship, from Ranbaxy to develop knowhow for chlorodiazopoxide and diazepam. I impressed on Dr Tilak that my approach to make the key intermediate 2-methylamino-5-chlorobenzophenone for diazepam would be different from the usual approach of making it by benzoylation of *p*-chloroaniline, (Chart V) and would work out much cheaper and more suitable for the Indian industry. He reluctantly approved my proposal and we initiated the programme to first complete the synthesis of the key intermediate which could then be converted easily to diazepam by a known approach.

While working on PL 480 scheme we faced the problem of procuring plant materials for further investigations. Although I was constantly writing letters to a Bombay trader, (late) Mr Thakkar, for the supply of these materials there was no response from him. In early 1972, I decided to personally visit him to procure the materials. Mr Thakkar was a supplier of senna to CIPLA and took me to Dr Y K Hamied, who was the Director of R&D. Dr Hamied was at the time trying to set up a bulk drug manufacturing unit at Vikroli. He enquired about my work at NCL especially in industrial project. I talked to him about my approach for the synthesis of 2-methylamino-5-chlorobenzophenone, starting from *p*-nitrochlorobenzene. He was very impressed and straightway told me that he was prepared to buy the knowhow which we worked out only on 100g scale in less than 3 months period. Within 2 weeks he visited NCL and had negotiations with Dr Tilak to finalise the deal for transfer of technology by paying a one-time fee of Rs 30,000. In fact, Dr Tilak and I were amazed at this development. I think it was one of the earliest NCL projects which went straight to industry for production without any problems. Subsequently, we completed out assignment on diazepam and it was released to Centaur Chemicals, Bombay who started manufacturing and have been supplying this product since then.

Although I was successful both in basic research and in my initial stint at industrial research I felt the need to spend one or two years at one of the best organic chemistry labs in US. This took me to EJ's group at Harvard. I enjoyed my stay with Corey's group working on one of the fascinating molecules of that time, the total synthesis of maytansine, an anti-tumour antibiotic (Chart VI). This kept me away from NCL between Sept 1975 and Sept 1977. On my return to NCL, I was determined to work on complex molecules especially in



MAYTANSINE

CHART VI

the area of antitumour antibiotics knowing fully well that several equipments were needed to carry out such a programme in India. I was not given proper working place and our PL 480 labs were occupied by the newly created dyes group. As I had no other option, I resorted to working in a small corner of my old lab. I also impressed on two former colleagues who had been assoicated with me earlier and were now posted in other groups, to work with me in their spare time. As I was not given either men or enough money to pursue my ambitions, I started looking for outside sources of financial help. One of my friends from Pune University told me that the Maharashtra State Government's Science & Technology Cell would be interested in funding projects of relevance to the State. Taking this cue I approached the State Science & Technology Department in Bombay. Dr Malshe, one of the senior project officers of the department helped me in this venture. He entrusted me with a proposal of isolating vinblastine and vincristine from *Vinca Rosea* leaves. India was the largest exporter of the dried leaves of *V. rosea* to US from which Eli Lilly was isolating vinblastine and vincristine, the two dimeric alkaloids used widely as anti-tumour agents. In fact, even today vincristine is the only drug for children's leukaemia and cures at least 50% of the cases. It is also used in combination with adriamycin and other anti-tumour agents for the treatment of various types of tumours. As India was the only exporter of *vinca* leaves at that time and some of the traders had started adulterating the dried leaves, Eli Lilly initiated their own plantation in Houston and also encouraged several African countries to grow *Vinca rosea* plants. This had prompted the Maharashtra State Government to take action to isolate and export vinblastine and vincristine, as otherwise the State was in danger of losing the benefits which nature had bestowed on it. Consequently, the State Government offered me Rs 2 lakhs to initiate this project. Subsequently, I also impressed on Dr Malshe the importance of initiating anthracyclines work which might lead to a new drug development for the treatment of cancer. I was fortunate to get an additional grant of Rs 3 lakhs for the adriamycin and its analogues project. This gave me the financial support needed to initiate both basic work on anthracyclines and industrial oriented work on *Vinca*. This programme was initiated in 1979 and within a year, we came out with a simple approach of isolating vinblastine from *V. rosea* totally devoid of chromatography. We optimised the process in the lab by extracting 40 kilos of dried *V. rosea* leaves and finally ending up with 10g of vinblastine B.P. Vinblastine was then subsequently converted to vincristine by oxidation with potassium permanganate (Chart VII). When we

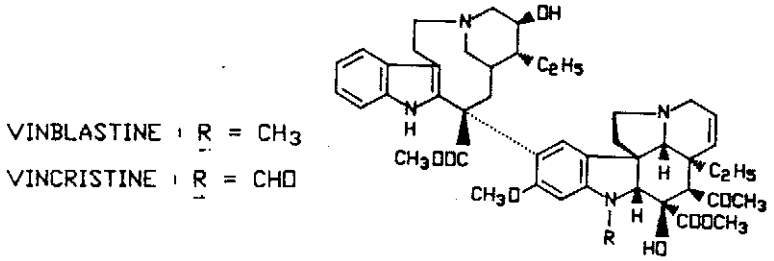


CHART VII

completed this process and submitted a report to the Maharashtra State Government in 1980, the then Chief Minister, Mr A R Antulay was astonished with our success and he made an announcement about vinblatine and vincristine developed at NCL on 29th July 1980 in the Maharashtra Vidhan Sabha. This news hit the headlines on the front pages of all the national newspapers of course, with a little bit of distortion, making it appears as if we for the first time had discovered vinblastine and vincristine for the treatment of cancer. However, the main text carried the actual view of my group's success in developing commercially viable technology for the isolation of vinblastine and its conversion to vincristine. This would serve not only to meet the Indian requirements but also for export to Western countries thereby earning foreign exchange. This would ultimately help the Indian farmers who normally cultivate *Vinca rosea* on wastelands. But some of the senior organic chemists in our country felt that we did not deserve the credit as there was nothing much in this technology which was well known in literature and as a result they were critical about my work. Although I had no role either in its announcement or later criticism but I must record that these organic chemistry experts of our country who had initiated this project several years before me and continued to work subsequently could not produce even 1 g of vinblastine. In subsequent years, I had to supply vinblastine to many individuals and institutions who were working on the isolation and identification of vinblastine in the total extract of *Vinca rosea* which contains more than 75 alkaloids.

In spite of the fact at we were very successful in finding a superior approach for the isolation of vinblastine and its conversion to vincristine, compared to what was being practised in US and other western countries we faced the problem of finding a suitable industry to exploit this technology. The Maharashtra Government was keen to give it to a public sector and that too preferably in the State, so we approached Hindustan Antibiotics, Pimpri for its exploitation. The then Managing Director though not showing any reluctance to accept the proposal but added the condition that vinblastine and vincristine should be formulated as vials and their bioefficacy should be established before he could make any firm commitment. For this, I had to make several trips to HAL, to formulate at least 200 vials of each of these drugs. I then had to approach the Tata Cancer Hospital, Bombay, for the clinical efficacy of these vials. The then Head of the Chemotherapy Unit, Dr Shetty was very cooperative and tried our vials on several patients and gave positive report on the efficacy. Even after establishing these facts, the M.D. of HAL was not willing to implement this project for reasons best known to them. I felt that HAL being an antibiotics plant with no expertise in plant products, it was not wise on our part to insist HAL to implement this project. Dr Doraiswamy also contacted some of the industries but everyone kept on looking into the statistics that were available on sales of vinblastine and vincristine in India. At that time, the sale of these two products together never exceeded Rs 20 lakhs per annum. As the industry has to create facilities for procuring the dried leaves of *Vinca* leaves from all over the country, storing and finally extracting large volumes, involving huge investments, several of them apprehensive with the financial viability of the proposal. Finally Dr Doraiswamy left the decision to me to

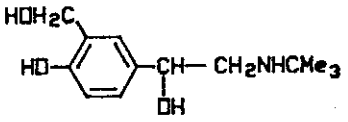
find the right industry for its implementation. As my contacts with CIPLA by then were firmly established, I tried to convince Dr Y K Hamied who was also reluctant for the same reasons to implement this project in CIPLA. At my insistence, he reluctantly agreed to implement it and the technology was passed on to CIPLA in 1983 through an agreement signed between CIPLA and the Maharashtra State Govt's Science & Technology Cell. Dr Hamied was very considerate and introduced this product in less than a year's time. The two products were launched in the country at a special ceremony at NCL on 2nd December 1983 by way of presenting the first lot of 500 vials to the Directors of 3 major cancer hospitals in this country (Tata Cancer Hospital, Bombay, All India Institute of Medical Sciences, Delhi and Govt. Cancer Hospital, Madras). CIPLA sold vincristine vials, each vial containing 1 mg of vincristine sulphate at a price of Rs 25 per vial. The imported vials were, at that time, sold at Rs 80 per vial of vincristine sulphate (no import duty on anti-cancer drugs). Realising the potential of vinblastine and vincristine for export to the western world where cancer was a major problem, CIPLA took the necessary measures and obtained FDA, US clearance to manufacture and export the drug to USA. For the last 3 years they have been regularly exporting not only to US but to all the western European countries thereby earning foreign exchange, while utilizing only indigenous raw materials in its manufacture. Today CIPLA is the sole industry manufacturing these two alkaloids in this country. There is ample scope to enhance its production for export but the main bottleneck is the non-availability of *Vinca rosea* leaves in sufficient quantities.

It may not be out of context to add that I had to face several problems after I returned from my Harvard training. I was demoted from a position of Scientist-E in PL-480 Scheme to a position of Scientist-C thereby entailing a financial loss of at least Rs 400 per month in addition to personal humiliation. At that time, Dr Y K Hamied invited me to CIPLA and pressed me to join CIPLA as R&D Director. He also went to the extent of stating that he would build a good R&D lab in Bangalore, a place which may be to my liking. He was very keen to have a person of his choice before he ventured to build a good R&D facility for CIPLA. Incidentally, he took over as the Managing Director of CIPLA from 1972 immediately after his father's death. He was keen on building up CIPLA's basic drug production capability for which he realised the importance of having a sound R&D facility. As I was reluctant to leave NCL, he asked me to be associated with CIPLA as an institutional consultant. This I readily agreed to as it would give me an opportunity to associate with a pharmaceutical industry rather than with dyes or other products and also it would compensate for the financial setback I had received. I started working as an institutional consultant to CIPLA from 1978 onwards and one of my first assignments was to work on salbutamol, an anti-asthamatic drug. Simultaneously, we initiated at CIPLA R&D at Vikroli the process development for the production of sulfamethoxazole. In fact, in less than 6 month's time we had worked out a process on a one-kilo scale. However, when it went on production for the first time at their Vikroli unit, several batches met with failure. This induced me to take permission from the Director, NCL and work on the plant with the R&D personnel. Within a week, we set everything right and its

production went on thereby saving time and reposing confidence in Dr Hamied. Things did not go well earlier as the production people were under the impression that R&D is only for tax benefits of the company and the M.D. had to bring tecnology from outside the country if it were to work on the plant. Incidentally, CIPLA was the first to produce sulfamethoxazole in the country. Subsequently, several companies, especially Standard Organics in Hyderabad, have taken up its production on a large scale. Today Hyderabad produces sulfamethoxazole for export to several countries all over the world.

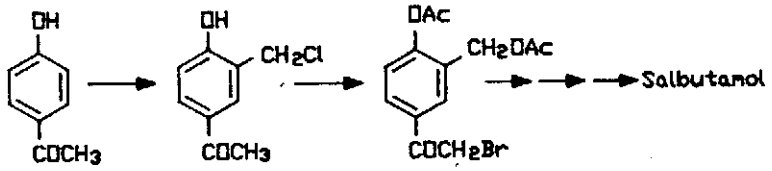
Salbutamol is a high-value, low-volume antiasthmatic.. It was administered as an inhalor and also in the form of oral tabs each containing 2 mg of salbutamol sulphate. It was introduced by Glaxo all over the world under the trade name Ventolin. As none of the product patents came in our way, we looked into the process development of salbutamol adopting some of the reagents which are normally confined to organic laboratories for doing fundamental research and are unheard of in this country as material for commercial production (Chart VIII). Even today, in many organic labs, handling 10 g of lithium-aluminium hydride is considered risky and we have to operate production utilizing 10 kg of lithiumaluminium hydride per batch. When salbutamol was intro-

SALBUTAMOL (ALBUTEROL)

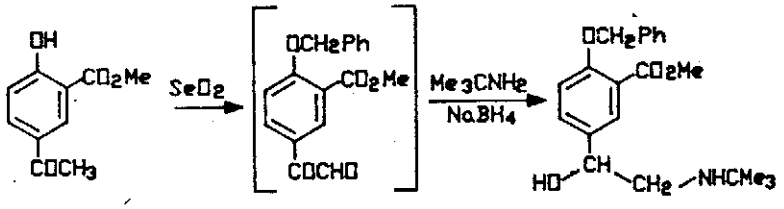


VENTOLIN (Glaxo, UK 1969
Other countries 1971 - 74)

1. GENERAL METHOD



2. CIPLA'S APPROACH



(CIPLA - 1979)

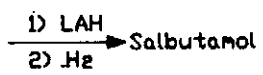


CHART VIII

duced by CIPLA in this country, they fought to keep Glaxo from introducing salbutamol formulation based on the imported basic drug. Ultimately, CIPLA succeeded due to the fact that it was indigenously producing salbutamol from the basic stage with CSIR's involvement. Therefore, Glaxo was denied the licence to sell salbutamol within the country at that time. This encouraged CIPLA to venture into many new products taking advantage of the new patent law and the confidence Dr Hamied had in us. In fact, I used to have several meetings with Dr Hamied from whom I learnt my first lessons in industrial research in basic drug manufacture. Even today, he is one of my great supporters and my association with CIPLA continues resulting in the introduction of several products from time to time which I would like to enumerate in the course of my lecture.

Subsequent to Dr Tilak's retirement, Dr Doraiswamy took over as the Director of NCL. He felt the need to appoint a Head of the Organic Chemistry Division which had remained vacant ever since Dr Sukh Dev had left NCL in 1973. The Scientist-F post was advertised in 1979 and I offered myself as a candidate despite the fact that I was then working as Scientist-C. When I approached Dr Doraiswamy to forward my application to CSIR, his first reaction was that I might not be called for an interview as there were several Scientists-EII and E-I who were senior to me within the organization and several outsiders were also likely to be considered for this prestigious position. I pointed out to Dr Doraiswamy that since the post was being advertised and if merit was the only consideration for selection, then I was confident of walking through the selection committee. He was a bit astonished at my confidence and assured me that merit would be the only consiederation for selecting the candidate and nothing else would come in the way of selection as he was keen to select the right person who would meet NCL's high standards. He assured me that he would forward my application. During the years 1979 and 1980, just before I faced the interview committee, I succeeded in publishing my work on anthracyclines (Chart XI). In addition, my success in isolating vinblastine and its conversion to vincristine coupled with the confidence that Dr Doraiswamy had in me, aided my selection as Scientist-F and Head of the Organic Chemistry Division in 1980.

In early 1981, when I had to submit my first research programme as Head of the Organic Chemistry Division, the main thrust was on anthracyclines and other anti-tumour agents along with the Vitamin B6 project. Dr Doraiswamy was not happy about reviving the Vitamin B6 project at NCL because it was one of NCL's failures in spite of the fact that the project had been initiated as early as 1958 and had continued till 1973. There were several reasons for its failure despite all efforts put from 1968 to 1973. NCL finally had to give it up. This had created considerable bitterness between NCL and IDPL as they were supposed to go into production of Vitamin B6 based on NCL knowhow. For this reason, Dr Doraiswamy was unwilling to revive this project. My interest in reviving this project was mainly because it was one of the early projects of the division which I happened to head and I would not want it to remain as a black mark in our minds. We worked for a year quietly with the approval of the Director and by the end of 1981 we were confident of making it a success.

We realised where my predecessors had gone wrong earlier and we succeeded in selecting a correct approach. Though it was our intention to pass on this knowhow to IDPL Hyderabad, we were unable to convince the IDPL R&D personnel of the advantages of initiating a joint programme. Mr Devarajan, the former M.D. of IDPL realised the potential of this project and recommended to Mr D B Gupta, the Managing Director of Lupin Laboratories to take up this project from us. My first few meetings with Mr D B Gupta and his senior colleagues resulted in the transfer of this technology to Lupin. Further, they agreed to put up a pilot plant at Aurangabad before they ventured to set up a 50 tonnes per year production plant at Ankleshwar. So from 1983 to 1985, my colleagues and I at NCL worked on this for several hours each day in close collaboration with the R&D and project team of Lupin. In 1986, M/s Lupin started producing Vitamin B6 and achieved an annual production of 40 tonnes by 1989. Today, Lupin is planning to double their production as Vitamin B6 is in short supply in the world market, a fact which has enhanced its price.

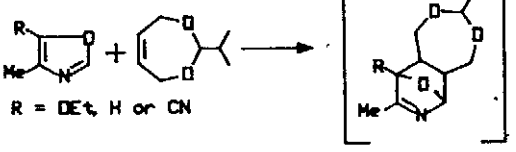
Vitamin B6 is one of the finest examples of innovations changing the entire technology from time to time, as is reflected in its price. The first commercial synthesis of Harris Folkers (Merck group) was successfully implemented in 1944 and Vitamin B6 was sold at a price of 1,000 US dollars per kilo. Subsequently, a number of alternative syntheses appeared which resulted in commercialization of this product by many companies including Hoffman La Roche in Switzerland and the price was stabilised at US dollars 460 per kilo in 1951. In the late 50s, an important and significantly shorter pathway was reported based on the original publication of Kondratyers from USSR in which it was shown that alkyloxazole reacted as dienes in Diels Alder condensation with maleic anhydride with the cleavage of the adduct to give pyridine derivatives. Harris and coworkers at Merck exploited this reaction and made Vitamin B6 employing 4-methoxy-5-ethoxyoxazole as the diene (Chart IX). A variety

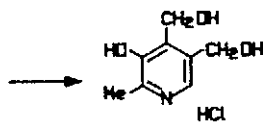
PYRIDOXINE HCl (VITAMIN B_6)

Commercial methods

a. Al2 step synthesis of Harris & Folkas (Science 1939)

b. Diels – Alder synthesis





Year	Bulk selling price (s/kg)
1944	1000
1950	515
1955	460
1960	80
1965	55
1970	30
1980	30
1991	50

CHART IX

of substituted oxazoles and dienophiles have been employed including the inactive dianophile, 2-*cis*-butene-1,4-diol. A host of variations on this procedure have been devised. As a result of these innovations, the price of Vitamin B6 touched rock-bottom at US dollars 30 per kilo by the year 1970. In subsequent years, even by 1980 the price did not go beyond US dollars 40 in spite of the fact that the prices of several intermediates have doubled during the years between 1970 and 1980. NCL scientists first worked out the 12-step synthesis and by the year 1963 they realised that it was obsolete. They switched over to the new Diels Alder approach. They worked out 4-methyl-5-ethoxyoxazole as the diene and perfected this technology to some extent. As the ethoxyoxazole is unstable, this approach was also met with several problems, resulting in the termination of the project. When we revived our interest in Vitamin B6, we rightly selected 4-methyl-5-cyanooxazole as the diene rather than the ethoxyoxazole and every aspect in developing its technology was studied to make the project a success. I strongly believe that any project initiated in a CSIR laboratory will not be successful unless there is a commitment and close collaboration from the industry personnel for technology development and the subsequent transfer to production. I must admire the way Lupin's R&D and project team worked with us resulting in the final success of the Vitamin B6 project. During the last one year the price of Vitamin B6 has gone up to US dollars 50 per kilo. This is mainly because the Merck plant working on the ethoxyoxazole has closed down due to reasons of economy, thereby creating a shortage of Vitamin B6 in the world market. I am glad that Lupin have already begun doubling their plant capacity.

At NCL I dealt with several other industrial projects, including process development for ibuprofen and certain beta-blockers such as metaprolol and atenolol. Ibuprofen was commercialised for the first time in the country by CIPLA (Chart X, Methods A&B). Subsequently, we also looked into different ways of improving this technology. Several industries in India have also started manufacturing this product because of its potential in both the domestic and export markets. Several industries in Hyderabad, especially Cheminor, an industry belonging to the group of Dr Reddy Laboratories came out with a different approach (Chart X, Method C) and subsequently Cheminor became the largest Indian producer and exporter of ibuprofen.

During my 4½ year tenure as Deputy Director and Head of the Organic Chemistry Division, I tried to establish a good school of organic synthesis and initiated several projects both in fundamental research and in applied areas. I was very choosy in selecting only those projects which had utilitarian value. For this reason, a major programme was initiated on anthracyclines. Adriamycin, belonging to this class of compounds was already approved by the FDA of the US as the drug of choice for the treatment of a wide variety of cancers. However, it suffers from the serious drawback of having cumulative dose dependent cardiotoxicity. Much effort has been directed towards obtaining new derivatives that show decreased side effects and/or increased anti-cancer activity. 4-Demethoxydaunomycin, one of the synthetic analogues, has been shown to be eight times more active and its clinical results are very promising. These facts have stimulated the synthesis of the aglycon portion of 4-demethoxydau-

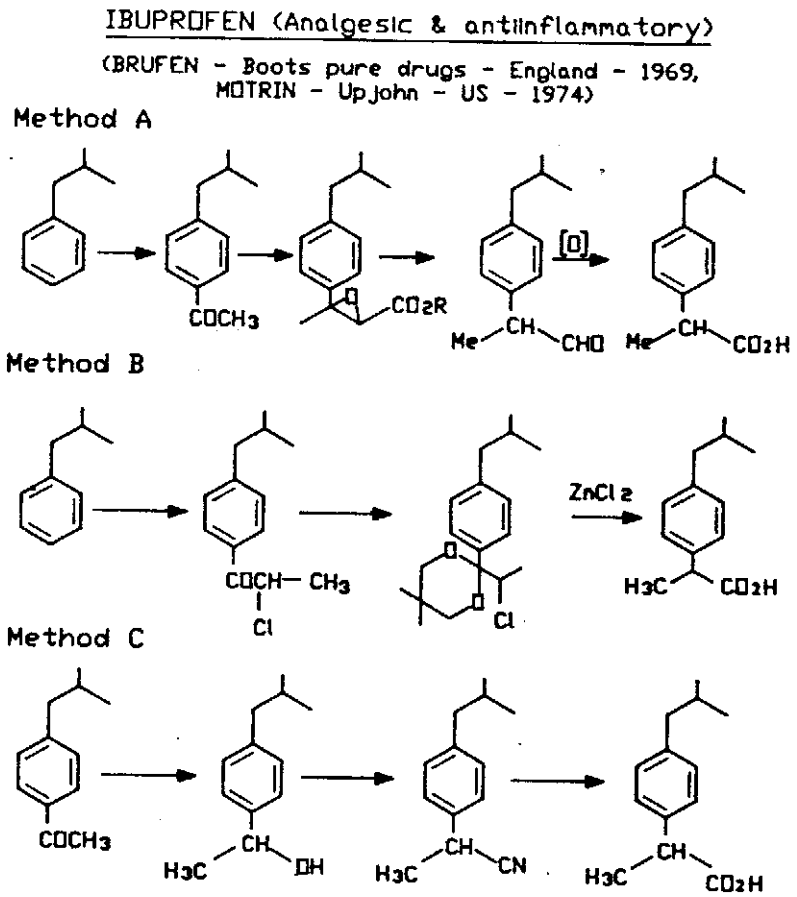
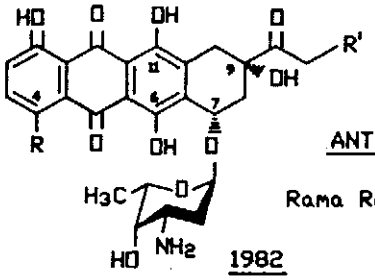


CHART X

nomycin. We are the only school to come out with several alternative approaches for the synthesis of the aglycone and the synthesis of L-daunosamine, the sugar part of these anthracyclines, so we could achieve its total synthesis. We published our findings by way of several communications in reputed international journals and they have been extensively cited (Chart XI). Even today I continue to hear from several pharmaceutical industries who still work on anthracyclinones that our methods are the best to adopt, if they need anthracyclinones in gram quantities.

Our work on anthracyclines had led us to look into other antitumour agents. One of the most fascinating of these was a molecule which appeared in 1982, a compound called fredericamycin-A which is an antibiotic isolated from the fermentation broth of *Streptomyces grieseus.* Preliminary reports in several journals and newspapers in US highlighted its unique properties as an anti-tumour agent. The presence of a novel and hitherto unknown spiro (4,4) nonane system, undoubtedly makes this molecule unique and so its total synthesis attracted the attention of several chemists. At one time, between 1984 and 1988, almost all the good schools in the USA were involved in attempts to synthesize fredericamycin-A. We were the first to develop the strategy for the construc-

ANTHRACYCLINES



ANTHRACYCLINONES

Rama Rao et al

1982		1983
Tet. Lett.	775	JOC, 1552
Tet. Lett.	1115	Tet. Lett. 24
Tet. Lett.	2415	Syn. Comm., 331
Tet. Lett.	3555	J. Chem. Comm., 546
Tet. Lett.	4373	Syn. Comm., 1249
		IJC, 521

Daunomycin R = OMe; R' = H

Adriamycin R = OMe; R' = OH

4-Demethoxy- daunomycin R = R' = H

1984

JCS.Chem. Comm. 453

IJC, 4643

Proc. Ind. Acad. Sci. 1059

L-DAUNOSAMINE

Carbohydrate Res., 1984, 469

Carbohydrate Res., 1984, 174

CHART XI

tion of the spiro (4,4) nonane system. Subsequently, more than 12 schools have reported different approaches for the synthesis of the spiro system but could go no further in its total synthesis. Only one total synthesis had appeared from US and we are the only other school to have completed its synthesis. In addition, we also looked into the synthesis of several hydroxy fatty acids and leukotrienes and their analogues as they offered interesting biological properties. We have also looked into several approaches for the synthesis of α-lipoic acid, a compound that has shown potential as an antidiabetic drug in the preliminary findings of Dr K K G Menon, the former Director of Hindustan Lever R&D Labs.

My earlier association with CIPLA as a consultant made me believe that success in industrial research depends on how closely we associate and work with the industry This led me to initiate projects only under sponsorship from industry and not as in-house projects. CIPLA, Bombay, was the first industry to sponsor several projects with me at NCL and many of them have gone successfully into production with the involvement of CIPLA's R&D and production people. I have already described the success of Vitamin B6, which was mainly due to the total commitment of the Lupin group.

I moved to Hyderabad on 15 July 1985 following my selection as Director of RRL-Hyderabad. My first task as Director of this laboratory was to close down several projects in the areas of coal, ceramics and inorganic chemistry and to give proper direction to the Institute. I felt the need to change the laboratory's name from the Regional Research Laboratory to something that would reflect the Institute's focus on chemistry and technology. I took advantage of Abid Husain Committee's visit and suggested to them that the name be changed to something, more appropriate, such as 'National Institute of Chemical Technology'. Mr Abid Husain and all other members especially, Professor M M Sharma, strongly endorsed my views and recommended to CSIR the change of name. Finally, the name was changed to the 'Indian Institute of Chemical Technology' effective from 1 April 1988. This gave a clear direction to the laboratory's work. I have strengthened our work on pesticides and initiated several projects in this area. We have also identified projects in the area of catalysis and speciality polymers especially on adhesives. Other major projects identified include cyanuric chloride which involves the reaction of HCN with chlorine to first obtain cyanogen chloride, which on trimerisation gives cyanuric chloride. We have put up a pilot plant on our site producing 10 kg/hr of cyanuric chloride under sponsorship from ATIC. Dr Kaiwar, M.D. of ATIC provided the necessary support for its success. The concept of bringing industry close to laboratory has been strengthened by way of initiating several sponsored projects resulting in cash earnings ranging from Rs 10 lakhs in 1984 to Rs 150 lakhs since 1988, year after year from private industry. I also impressed on several of my colleagues the need to initiate fundamental research in the areas of organic chemistry, catalysis and all other branches of chemistry and chemical engineering. My efforts have not been in vain as it is apparent that IICT has become a centre of excellence in organic chemistry and catalysis. This is borne out from our numerous publications in several international journals. Many of our young scientists have received year after year the 'CSIR Young Scientist' awards and two of my colleagues have for the first time got the Bhatnagar awards in chemical sciences for the years 1990 and 1991.

Ever since I was a student at NCL, I used to spend more than 12 hours a day on research including Saturdays and holidays except some Sundays. This practice is being continued even at IICT. When I was about to leave NCL to take over the Directorship of RRL-Hyderabad, Dr Doraiswamy, whom I consider as my mentor during the years 1980-85 had cautioned me that I might have to give up research as most of my time would be required to be spent on administration. I assured him that I would like to keep my research interests alive in spite of the administrative work as the Director at RRL-Hyderabad. When I came to Hyderabad, my first concern was to have a small lab of my own so that I could shift some of my research fellows to Hyderabad who were working with me at NCL. As space was the main constraint in RRL, I converted some of the old pilot plant sheds into organic laboratories and then started working on several areas of interest both in fundamental and applied chemistry. I felt my expertise in drug technology, which was built up during my stay at NCL, should continue to grow and the drug industry also responded favourably by sponsoring several projects with my personal involvement. In fact, I

have been very choosy in selecting the projects and I generally weigh several factors including national interest. I would like to enumerate some of the areas we initiated which reflect my desire to strengthen the Indian drug industry by our association.

Contributions to Indian Drug Industry from IICT

My personal group initiated several projects sponsored by various Indian drug industries. CIPLA continued to associate in a major way with us. One of the earliest projects which we completed and transferred to them is Norflaxacin. It is a first fluroquinolone that went into commercial production at their Bangalore unit in 1987. Subsequently they have also commenced production of ciprofloxacin which offered several advantages over Norfloxacin (Chart XII).

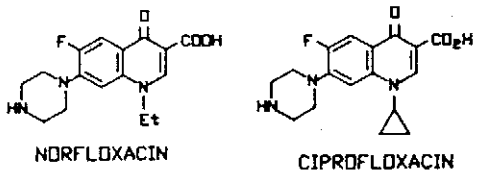


CHART XII

For CIPLA we have also looked into technology development for the antitumour agent Etoposide. Etoposide is a broad anti-tumour agent introduced by Sandoz in 1983 and is now marketed world over by Bristol-Myers for the management of small cell lung cancer, malignant lymphous, acute leukaemias, testicular tumours, bladder cancer and trophoblastic diseases. It is also commonly used in combination therapy with other chemotherapeutic agents. Etoposide is a semi-synthetic product derived from photophyllotoxin which is obtained from the Indian tree *Phodophyllum emodii. Phodophyllum emodii* is grown widely in the Himalayan region of Jammu & Kashmir and Himachal Pradesh. The roots of *Photophyllum emodii* contain 1% of photophyllotoxin. India is a regular exporter of the roots and resin of photophyllum (containing 40% phodophyllotoxin) to Europe, where it was finally converted into etoposide. The technology converting photophyllotoxin to etoposide was perfected in our laboratoriesx through several intricate chemical reactions (Chart XIII). It was

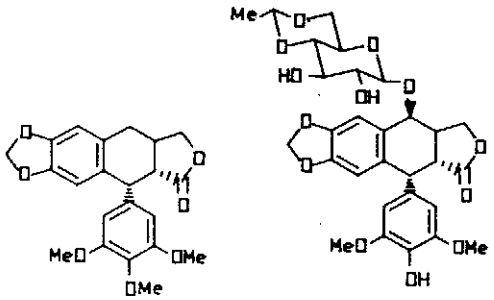


CHART XIII

passed on to CIPLA's Bangalore unit in 1990. The technology was further perfected on the plant and introduced in July this year. Each vial contains 100 mg of etoposide. In the past few months they have been selling 10,000 vials per month at a cost of less than half of the price of the imported vials sold in India. In addition, we have perfected omeprazole, a drug which inhibits acid producing proton pumps in the parietal cells bringing faster relief for ulcer patients. CIPLA commercialised this product from this year.

AIDS (Acquired Immuno Defficiency Syndrome), caused by the HIV virus is being transmitted at an alarming rate in India, especially through prostitution in Bombay and other major cities. The new curative agent for the treatment of AIDS, Azidothymidine (AZT) (also known as zudovuidin) was found to be effective in inhibiting viral replication thereby prolonging life expectancy and reducing the risk of secondary infection in the AIDS patients. Each capsule of AZT in US costs 3 dollars and a patient has to take 3-4 capsules per day for prolonging his life, which then becomes exhorbitantly expensive. We have initiated and completed a simplified approach for the production of AZT and based on this technology CIPLA will go into its production soon. Dr Y K Hamied assured me that they would produce this drug and sell it in the Indian market at production cost with no profit for them. In addition we have also passed on this technology to Lupin and to Dr Reddy's Laboratories with a view to exporting this drug to the rest of the world. We have also initiated technology development for DDI and hope to complete it soon (Chart XIV).

DRUGS FOR AIDS

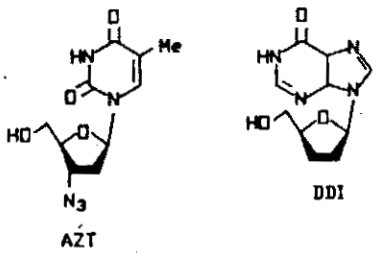


CHART XIV

We have also initiated several other products for commercial production.

The first product introduced by FDC based on IICT technology is Flurbiprofen, an analgesic effective at half-dose compared to Ibuprofen and offered several advantages over other propionic acid derivatives. They started its commercial production from 1989 and are now exporting to several countries including Japan. FDC is formulating Timolol maleate for the treatment of gluacoma (Chart XV). The basic drug was imported at a price of Rs 220 per gram (including duties) and Indian consumption varied between 15-20 kilos per year. We looked into its synthesis by utilising asymmetric synthesis (which I keep referring as chiral technology) starting from D-Mannitol. We perfected the process in collaboration with their R&D group and the product was commercialised in 1990 by FDC not only to meet their own captive production but to export this expensive drug in a major way worldwide. In fact they are getting

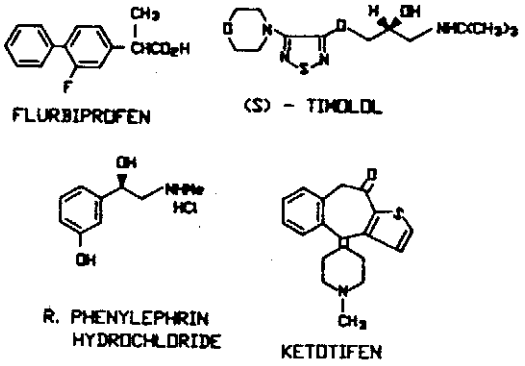


CHART XV

several orders at a price of 4000 dollars per kilo. We have also initiated other products for FDC which include phenylefrine and ketotefin. The former is being imported in large tonnage and has great export potential. IICT has already completed and transferred this technology which is likely to go into production from the end of 1992.

We have initiated several major products for Lupin. Mr D B Gupta, Chairman and Managing Director has signed an agreement on 1st April, 1990 to sponsor projects worth Rs. 100 lakhs for various drug products for a period of 3 years. We worked out betablockers, especially Nodolol, by an elegant approach and Metoprolol starting from phenol with a view to exporting these two drugs by Lupin to US and other countries (Chart XVI).

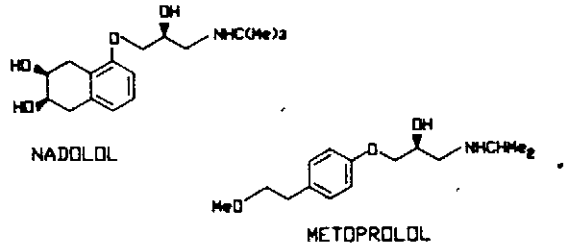
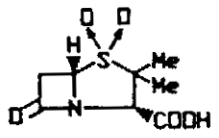


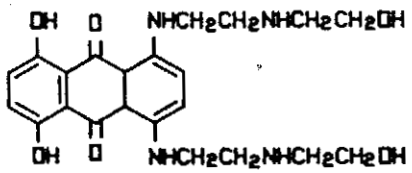
CHART XVI

Technology development for several other products has been initiated including Vitamin-A which was earlier sponsored by Glaxo India Limited. Recently, we have passed on the technology for ketorolac, a new analgesic which is likely to be introduced in India in the next few months. Several other products including antibacterials and cardiovascular drugs are in the pipeline.

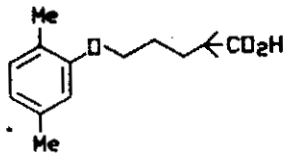
Other products that have been completed and are at different stages of commercial production include sulbactam (beta-lactamase inhibitor) for Unichem, Mitoxantrone (anti-tumour agent used especially for breast cancer) for Sun Pharmaceuticals, Gemfibrozil (cholesterol lowering) and Astemizole (Anti-histaminic) for Cadila laboratories (Chart XVII).



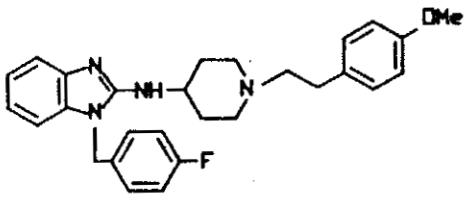
SULBACTAM



MITOXANTRONE



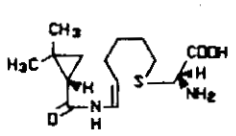
GEMFIBROZIL



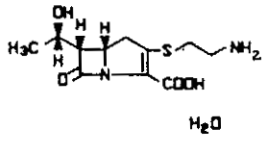
ASTEMIZOLE

CHART XVII

In addition more than 20 products are under sponsorship by various Indian industries. We have initiated in a major way the process development for quinolones, semi-synthetic Cefalosporins including the latest carbapenem (primaxin) (Chart XVIII) whose cost is exorbitant for the Indian market.



CILASTATIN
(DHP-I INTRIBITOR)



IMIPENEM

Mixture of imipenem and cilastatin is marked under the trade name Primaxin in the US and tienam in other countries

CHART XVIII

Although Indian industry on its own and in association with CSIR laboratories have introduced several new drugs in this country, many of these are produced from imported intermediates. The number of intermediates that are being imported continue to increase, thereby enhancing our foreign exchange bill. Some selected examples include, 2-aminobutanol for ethambutol, trimethoxybenzaldehyde for trimethoprim and phenylglycine and *p*-hydroxyphenylglycine for ampicillin and amoxicillin respectively. Ethoxymethylene diethylmalonate and novaldiamine for chloroquine are imported in several hundreds of tonnes. We have launched in a major way on priority the development of technologies for some of these intermediates. We have perfected trimethoxybenzaldehyde from *p*-cresol for Bombay Drug House and phenylglycine and *p*-hydroxyphenylglycine for SOL, Hyderabad, Armour Chemicals, Bombay and Cadila Labs, Ahmedabad. We are now looking into various chlorofluoro aromatics required for a variety of quinolones under sponsorship from Navin Fluorines. It is our

endeavour to see that most of the drug intermediates that are now being imported are made available within India in the next 2-3 years. We have also launched in a major way technology development based on carbonmonoxide reactions. For example we have already perfected on bench scale the production of diethyl malonate from ethylchloro acetate by reacting carbonmonoxide in ethanol medium using cobalt carbonyl as a catalyst. This approach also has been applied to obtain phenyl acetic acid from benzyl chloride. We are now setting up a pilot plant to perfect these carbonmonoxide based technologies.

Basic Research

I believe strongly that unless scientists contribute to the advancement of knowledge, it will not be possible to develop technologies in an efficient manner. I always insist that good science alone will lead to good technology. Son one of our goals is to build the capability in our young organic chemists to become future leaders of various research organizations and university departments. To this end, we have initiated several projects which are of relevance to both national and international interests. They include the synthesis of anti-tumour agents, such as anthracyclines, fredericamycin, sesbanimide, cervinomycin, aranarosin (Chart XIX) and other which have been proved to be of clinical

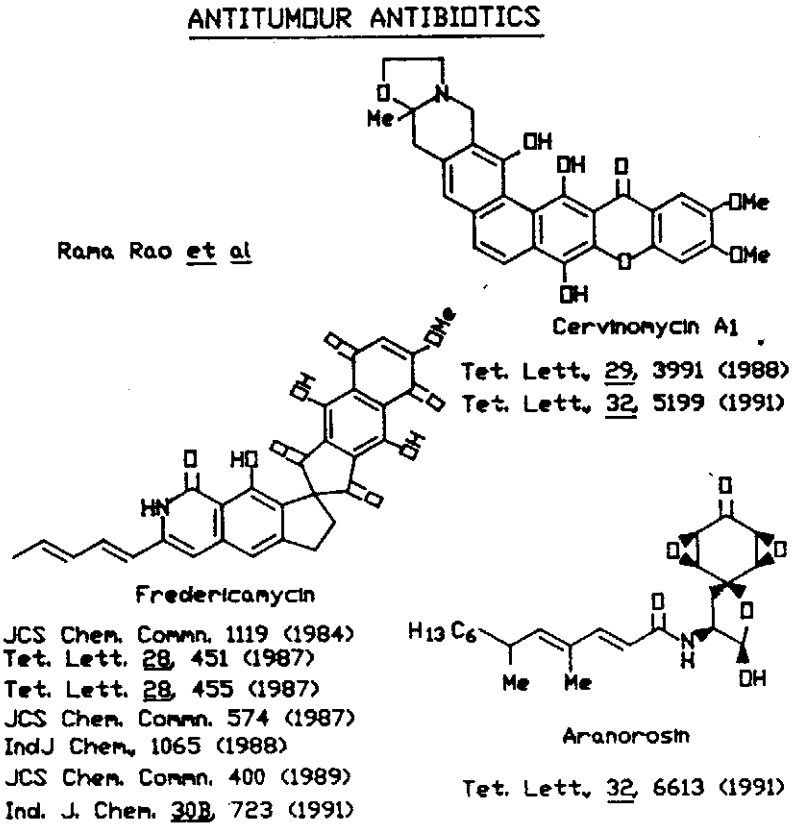
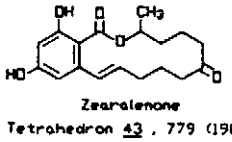


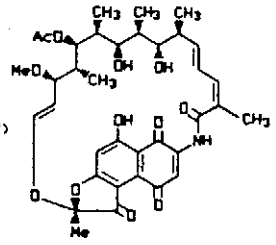
CHART XIX

interest. We also initiated a programme on macrolides and successfully completed the synthesis of zearalenone and jaspamide in addition to the synthesis of *ansa* chain of rifamycin-S (Chart XX). Recently we have been involved in

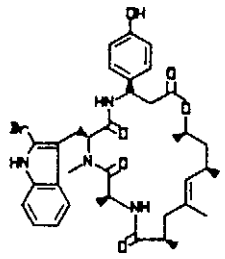
MACROLIDES



Zearalenone
Tetrahedron 43 , 779 (1987)

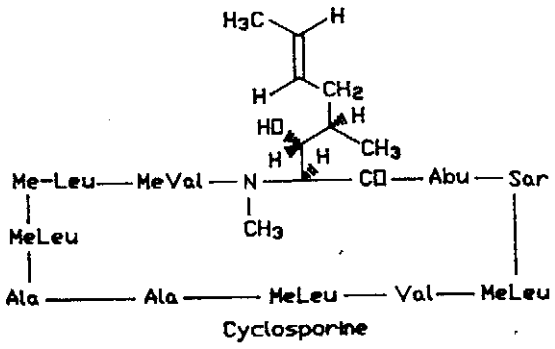


Rifamycin-S
JCS Chem. Comm. 55 (1985)
Tet. Lett. 27 , 3297 (1986)

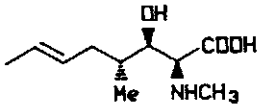


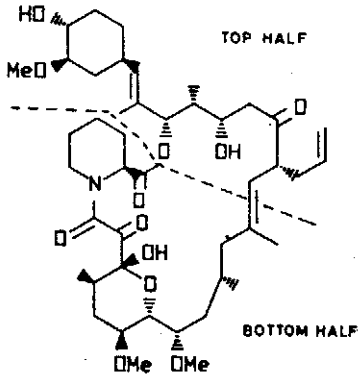
Jaspamide
Unpublished

CHART XX



Cyclosporine





FK-506

(4R) - 4 - [(E) - 2 - butenyl] -4, N - dimethyl-
L - threonine (MeBmt)

CHART XXI

the synthesis of cyclosporin, the only drug used as an immunosuppressant for those who have undergone organ transplantation. It is an extremely expensive drug supplied by Sandoz, Basel and it costs a patient in India at least Rs 50,000 per annum and the patient has to take this drug for his survival

throughout his life. Cyclosporin is an undecapeptide and the unusual amino acid MeBMT present in it is responsible for its activity. We came out with several approaches for MeBMT synthesis in order to synthesise this product in gram quantities (Chart XXI). Recently, a new antibiotic FK-506 isolated from *Streptomyces tsukubaensis* that was shown to be 100 times more active as an immunosuppressant compared to cyclosporin. It has attracted worldwide attention both for its chemical and biological activity. The compound is a 23-membered lactone with 14 asymmetric centres and its synthesis poses a challenge to organic chemists. Several prominent schools all over the world have initiated its total synthesis and only the best schools in US have partly succeeded in building the top and bottom fragments of FK 506. The Merck group in US are the first to report its total synthesis. We were the only school outside the US to complete the top and bottom fragments of FK-506 and are actively pursuing its total synthesis.

I have enumerated a few examples from my personal experiences in capability building in organic synthesis. Organic molecules are very complex and can pose an intellectual challenge to many of my young colleagues. Both the fundamental research and applied products such as those which have been initiated in my personal groups first at NCL and now in IICT have high scientific content. In the case of basic research, we have always published their results in the best of the international journals and in the case of applied programmes we filed several patents as many of these approaches represent significant scientific inventions. More than 40 organic chemists and chemical technologists have so far obtained their PhD degrees working in our basic and applied programme.

Conclusion

When I started my career in the early 60s, I was given the impression that basic research calls for intellectual exercise and industrial research is a mediocre exercise. In fact, the barriers were created by our academicians who have no knowledge about industrial research. It is always worthwhile to initiate a project which is of great potential for human welfare rather than diverting our valuable resources to areas which have no consequence in nation building other than training some PhDs. I have also realised that development of technologies for industrial purposes calls for extremely innovative research and requires the combined involvement of a team of organic chemists, process engineers and design engineers. If one has to work in this area he has to develop a project purely by his own efforts as there are no books or journals on the subject. Neither it is taught in any of our chemistry courses. In fact, it encompasses the whole area between research and manufacture – and generally we have been considering this branch as a poor career option. Today, Indian industry is in dire need of good chemists with a better knowledge of chemical development to head their R&D organizations. I have also realised that industrial research is not a repetition of what is already known in the literature but actually depends on discovering a new synthetic route which can be optimised to yield 90% efficiency at every step. The chemist who undertakes such exer-

cises should have the creative imagination to anticipate various problems associated with the transfer of any technology to commercial production in the industry.

I have tried my best to give an account of myself, and of the circumstances which have compelled me to initiate industrial research and good basic research to survive as a chemist in CSIR which aims to carry out good science of relevance to national needs. Good science does not arise unless we probe into problems of current interest. I have always tried my best to strike a balance between fundamental and applied research and applied research – a fact which ultimately helped me training several youngsters, many of whom have now settled in US. I hope that this lecture will provoke several of my organic colleagues to change their attitude towards applied research and also impress upon youngesters the need to understand industrial research in addition to pursuing their scientific goals so that they become worthy and productive citizens of this country.

Acknowledgement

I am indebted first and foremost to my former teacher, the late Professor K Venkataraman who taught me the principles of organic chemistry especially the chemistry of natural products and synthetic dyes and inculcated in me sincerity and hardwork and devotion to duty. I was associated with him for 15 years (1960-75) and published more than 70 papers. I have also on several occasions differed with his views in carrying out fundamental research and for not paying any attention to industrial research.

I am equally indebted to Professor E J Corey, Noble Laureate, Harvard University, who gave me an opportunity to spend 2 years in his group (1975-77). My association with him made me think big and select problems of a complex nature and of relevance to future programmes.

I am grateful to Dr Y K Hamied, Managing Director of CIPLA, who initiated me into the pharmaceutical industry. I learnt from him several aspects right from the selection of a project upto its implementation. Several of my projects have been exploited by CIPLA because of his constant backing and encouragement. Even today he is a source of inspiration for my involvement in industrial research.

Dr Doraiswamy, the former Director of NCL, was responsible for my growth as a chemist and administrator by giving my carrier a fillip during the period 1980 to 1985.

I am equally indebted to three persons who have inspired me in my research pursuits. They are, Professor C N R Rao, Professor M M Sharma and Dr S Varadarajan and I always respect them for their support and encouragement in my research ventures.

I would also like to place on record the support which I have received from several people from industry. Special thanks to Mr D B Gupta, Chairman and Managing Director, Lupin Laboratories, who was responsible for implementing the Vitamin B6 project and who continues to support us in a major way by sponsoring projects.

Several industries have sponsored research and backed me with liberal funding for my excursion into industrial research. I am grateful to all the M.Ds. (Poona Synthetics, Pune; Sudarshan Chemical Industries, Pune; Centaur Chemicals, Bombay; FDC, Bombay; Unichem Laboratories, Bombay; Armour Chemicals Ltd., Bombay; Dr Reddy's Laboratories, Hyderabad; Standard Organics Ltd., Hyderabad; Cadila Laboratories Ltd., Ahmedabad; Sun Pharmaceutical Industries, Baroda) of these companies for their gesture.

Last but not least I extend my gratitude to all the young colleagues who joined me to pursue their research career and worked day and night on projects concerning basic and applied research. They deserve all the credit. I am also thankful to my senior colleagues who have helped me in many ways by their involvement in planning and execution.

Finally I am thankful to all those who have quietly worked behind scenes both at NCL and presently at IICT for my success.